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(54) Title: METHOD OF PREPARING SALICYLOYLAMINO ACIDS

(57) Abstract

A method for preparing salicyloylaminos acids is provided. An oligosalicylate and an amino acid are reacted to yield the salicyloylaminos acid.

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METHOD OF PREPARING SALICYLOYLAMINO ACIDS

FIELD OF THE INVENTION

The present invention relates to methods for preparing salicyloylamino acids. Certain salicyloylamino acids are useful in the delivery of active agents, such as for example, biologically or chemically active agents, to a target.

BACKGROUND OF THE INVENTION

Certain salicyloylamino acids have been demonstrated as being useful in the delivery of active agents, particularly, through the oral route. See, for example, U.S. patent application serial no. 08/414,654, filed March 31, 1995.

Two methods of preparation of such compounds are illustrated in U.S. patent application serial no. 08/414,654, filed March 31, 1995 and provisional U.S. patent application serial no. 60/003,111, filed September 1, 1995.

Additionally, Ho et al., *Synthetic Communications*, 26(14), 2641-2649 (1986) summarizes a number of methods for the preparation of ω -aminoalkanoic acids. These methods include the introduction of an amine group by the conversion of a ketone to an oxime or a carboxylate to a nitrile, followed by reduction by azidide opening of an anhydride, followed by Schmidt rearrangement, or by Hoffman rearrangement of an amide with aqueous base and bromine. Boc protected and N-acylated ω -amino alkanoic acids can also be obtained by hydrolysis of the N-Boc and N-acylated lactams, respectively. Ho et al. presents an additional synthetic route to N-Boc protected or Boc-amino acid coupled with ω -aminoalkanoic acids.

However, there is still a need for an efficient, economical, and commercially practical method for the preparation of salicyloylamino acids.

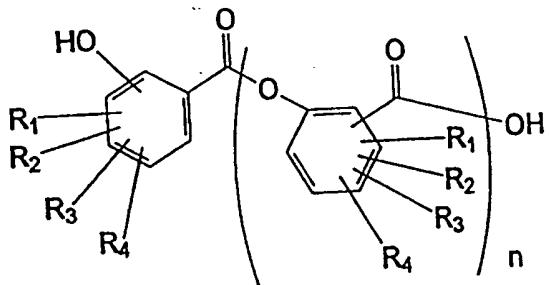
5 SUMMARY OF THE INVENTION

A method for preparing a salicyloyl amino acid is provided in which an oligosalicylate and an amino acid are reacted to yield the salicyloyl amino acid.

10 DETAILED DESCRIPTION OF THE INVENTION

Oligosalicylates are typically represented by the formula

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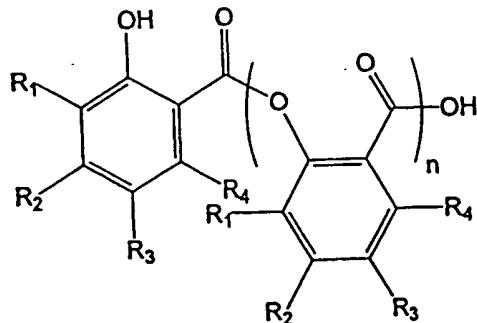
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wherein R₁, R₂, R₃ and R₄ are independently hydrogen, fluorine, chlorine, bromine, iodine, C₁₋₉ linear or branched chain alkyl, C₁₋₉ linear or branched chain alkoxy, C₆₋₁₄ aryl, C₆₋₁₄ aryloxy or 25 (C₆₋₁₄ aryl) (C₁₋₉ linear or branched chain alkyl); and wherein n is an integer from about 1 to about 10.

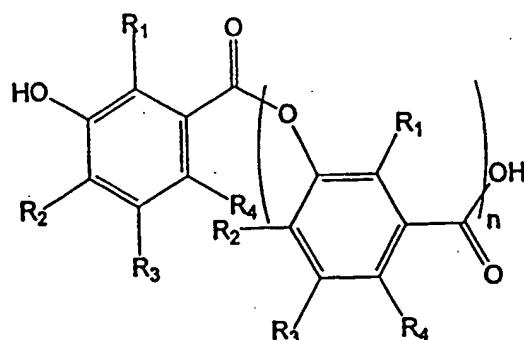
Preferred oligosalicylates are represented by the formulae

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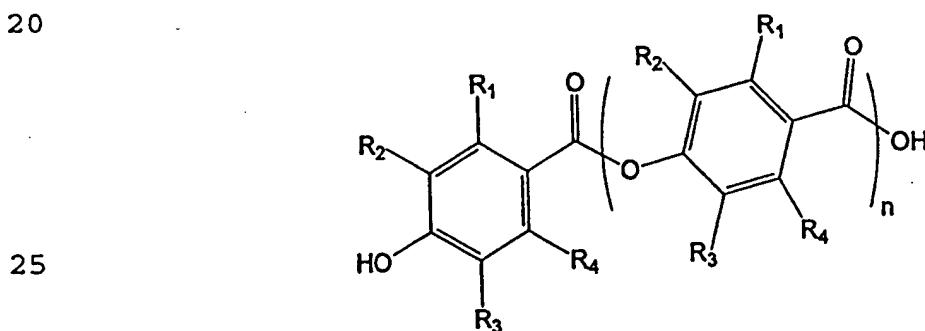
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wherein R₁, R₂, R₃ and R₄ are independently hydrogen, fluorine, chlorine, bromine, iodine, C₁₋₉ linear or branched chain alkyl, C₁₋₉ linear or branched chain alkoxy, C₆₋₁₄ aryl, C₆₋₁₄ aryloxy or (C₆₋₁₄ aryl) (C₁₋₉ linear or branched chain alkyl); and wherein n 5 is an integer from about 1 to about 10;



15 wherein R₁, R₂, R₃ and R₄ are independently hydrogen, fluorine, chlorine, bromine, iodine, C₁₋₉ linear or branched chain alkyl, C₁₋₉ linear or branched chain alkoxy, C₆₋₁₄ aryl, C₆₋₁₄ aryloxy or (C₆₋₁₄ aryl) (C₁₋₉ linear or branched chain alkyl); and wherein n is an integer from about 1 to about 10; and



wherein R₁, R₂, R₃ and R₄ are independently hydrogen, fluorine, chlorine, bromine, iodine, C₁₋₉ linear or branched chain alkyl, C₁₋₉ linear or branched chain alkoxy, C₆₋₁₄ aryl, C₆₋₁₄ aryloxy or (C₆₋₁₄ aryl) (C₁₋₉ linear or branched chain alkyl); and wherein n 30 is an integer from about 1 to about 10.

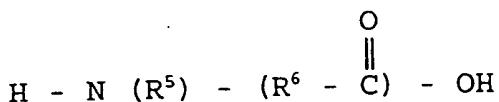
Most preferred oligosalicylates are oligosalicylate, oligo-methyl salicylate, and oligo-dichlorosalicylate.

An amino acid is any carboxylic acid having at least 35 one free amine group and includes naturally occurring and synthetic amino acids. Many amino acids and amino acid esters are readily available from a number of commercial sources such

Co. (St. Louis, MO, USA); and Fluka Chemical Corp. (Ronkonkoma, N.Y. USA).

Representative, but not limiting, amino acids for use in the present invention are generally of the formula

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wherein: R^5 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, or $\text{C}_2\text{-C}_4$ alkenyl;

15 R^6 is $\text{C}_1\text{-C}_{24}$ alkyl, $\text{C}_2\text{-C}_{24}$ alkenyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, phenyl, naphthyl, $(\text{C}_1\text{-C}_{10}$ alkyl) phenyl, $(\text{C}_2\text{-C}_{10}$ alkenyl) phenyl $(\text{C}_1\text{-C}_{10}$ alkyl) naphthyl, $(\text{C}_2\text{-C}_{10}$ alkenyl) naphthyl, phenyl ($\text{C}_1\text{-C}_{10}$ alkyl), phenyl ($\text{C}_2\text{-C}_{10}$ alkenyl), naphthyl ($\text{C}_1\text{-C}_{10}$ alkyl), or naphthyl ($\text{C}_2\text{-C}_{10}$ alkyl) or naphthyl ($\text{C}_2\text{-C}_{10}$ alkenyl);

20 R^6 being optionally substituted with $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_2\text{-C}_4$ alkyenyl, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{OH}$, $-\text{SH}$, $-\text{CO}_2\text{R}^7$, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_3\text{-C}_{10}$ cycloalkenyl, heterocycle having 3-10 ring atoms wherein the hetero atom is one or more of N, O, S, or any combination thereof, aryl, $(\text{C}_1\text{-C}_{10}$ alk)aryl, ar($\text{C}_1\text{-C}_{10}$ alkyl) or any combination thereof;

25 R^6 being optionally interrupted by oxygen, nitrogen, sulfur, or any combination thereof; and R^7 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, or $\text{C}_2\text{-C}_4$ alkenyl.

30 The preferred naturally occurring amino acids are alanine, arginine, asparagine, aspartic acid, citrulline, cysteine, cystine, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, ornithine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, hydroxy proline, γ -carboxyglutamate, phenylglycine, or O-phosphoserine. 35 The preferred amino acids are arginine, leucine, lysine, phenylalanine, tyrosine, tryptophan, valine, and phenylglycine.

The preferred non-naturally occurring amino acids are β -alanine, α -amino butyric acid, γ -amino butyric acid, γ -(aminophenyl) butyric acid, α -amino isobutyric acid, citrulline, ϵ -amino caproic acid, 7-amino heptanoic acid, β -5 aspartic acid, aminobenzoic acid, aminocaprylic acid, aminophenyl acetic acid, aminophenyl butyric acid, γ -glutamic acid, cysteine (ACM), ϵ -lysine, ϵ -lysine (A-Fmoc), methionine sulfone, norleucine, norvaline, ornithine, d-ornithine, p-nitro-phenylalanine, hydroxy proline, 1,2,3,4,-10 tetrahydroisoquinoline-3-carboxylic acid, aminodecanoic acid, and thioproline. Most preferred amino acids are aminocaprylic acid and aminodecanoic acid.

Poly amino acids are either peptides or two or more amino acids linked by a bond formed by other groups which can 15 be linked, e.g., an ester, anhydride or an anhydride linkage. Poly amino acids can be homo- or hetero- poly amino acids, and can include natural amino acids, synthetic amino acids, or any combination thereof.

Peptides are two or more amino acids joined by a 20 peptide bond. Peptides can vary in length from di-peptides with two amino acids to polypeptides with several hundred amino acids. See, Walker, Chambers Biological Dictionary, Cambridge, England: Chambers Cambridge, 1989, page 215.

The present reaction is typically conducted in an 25 aqueous medium (which can contain sodium hydroxide) and in the presence of one or more organic solvents such as, for example, dioxane, xylenes, acetonitrile, tetrahydrofuran, and 1-methoxy-2-propanol. Preferred reaction temperatures range from about 25 degrees C to about 150 degrees C. Preferred reaction times 30 range from about 0.5 to about 24 hours. Typically, the molar ratio of the oligosalicylate reactant to the amino acid reactant will range from about 0.5 to about 2.0.

The reaction product can be isolated from the reaction mixture by, for example, filtration followed by drying 35 of the filtrate.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

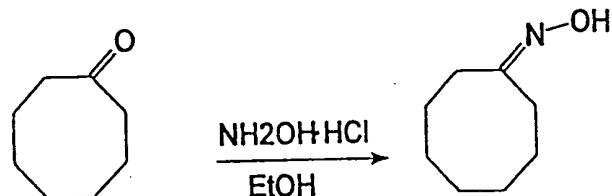
The following Examples illustrate the invention without limitation. All parts are given by weight unless otherwise indicated.

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Example 1 - Preparation of N-(salicyloyl)-8-aminocaprylic acid

A. Preparation of Cyclooctanone Oxime Hydrochloride

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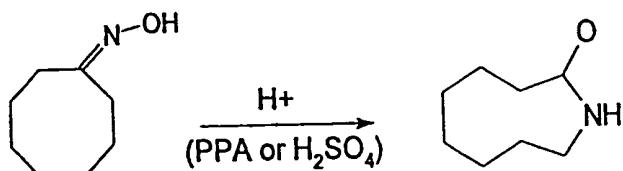
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Cyclooctanone (50 g, 0.396 mol, 1.0 eq) and ethanol (250 mL) were placed in a 500 mL round bottom flask equipped with a magnetic stir bar. Hydroxylamine hydrochloride (28.91 g, 0.416 mol, 1.05 eq) was added slowly. The cloudy reaction mixture was stirred at 25 degrees C for 20 min and heated to 20 50 degrees C for 30 min, during which time it turned clear. Upon cooling to 25 degrees C, the mixture was concentrated to produce an off-white solid, which still contained a small amount of ethanol. The cyclooctanone oxime was used without further purification.

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B. Preparation of 2-Azacyclononanone

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Cyclooctanone oxime (5.6 g, 39.6 mmol, 1.0 eq) and formic acid (15 mL) were placed in a 100 mL round bottom flask equipped with a magnetic stirrer, a cold-water condenser and a nitrogen purge. The mixture was treated with concentrated sulfuric acid (2.1 mL, 39.6 mmol, 1.0 eq) and heated to reflux. After 3.5 hours, no starting material was observed by TLC. The

now black reaction mixture was cooled to 25 degrees C and poured slowly into 200 mL of ice water. The pH was adjusted to 7.5-8.0 with 10N NaOH. The aqueous mixture was extracted with chloroform (3 times).

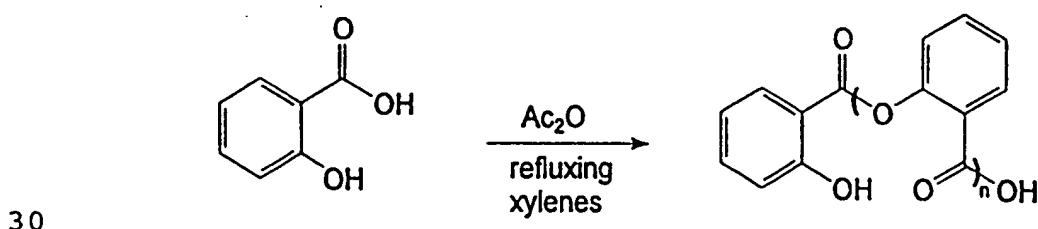
5 The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by Kugelrohr distillation. The 2-azacyclononanone was isolated as a colorless liquid (3.76 g, 75%).

10 C. Preparation of 2-Azacyclononanone

Polyphosphoric acid (31.9 g) and water (3.75 g) were placed in a 100 mL round bottom flask equipped with a stir bar and a cold water condenser. The mixture was heated to 130 degrees C, and cyclooctanone oxime (5.9 g, 35 mmol, 1.0 eq) was 15 added in small portions over 10 min. The oxime dissolved readily. The reaction mixture was stirred at 130 degrees C for 1 hour, turned dark, was cooled to 100 degrees C, and poured into 100 mL of ice water. The aqueous mixture was extracted with chloroform (3 x 75 mL). The combined organic layers were 20 dried over Na_2SO_4 and concentrated in vacuo. The 2-azacyclononanone slowly crystallized into an off-white solid (4.69 g, 94%).

25 D. Preparation of Oligosalicylate

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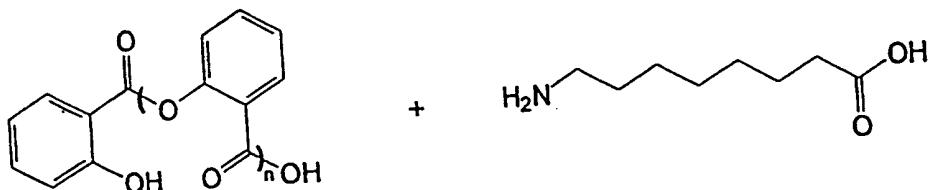


the volatile organics (xylanes and acetic acid) distilled into the Dean-Stark trap over three hours (135-146 degrees C). Distillation was continued for another hour (a total of 75 mL distilled), during which the pot temperature slowly rose to 195 degrees C and the distillate slowed to a trickle. The residue was poured off while still hot into an aluminum tray. Upon cooling a brittle yellow glass formed. The solid was ground to a fine powder. The 18.95 g of oligosalicylate produced was used without further purification.

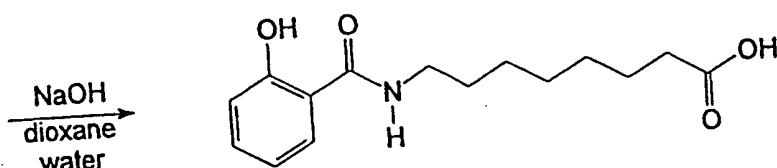
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E. Preparation of Salicyloylamino acid

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A 10 N sodium hydroxide solution of (4.4 mL, 44.0 mmol, 1.18 eq), 8-aminocaprylic acid (5.93 g, 37.2 mmol, 1.00 eq), sodium bicarbonate (0.88 g, 10.4 mmol, 0.28 eq) and water (5 mL) were added to a 250 mL round bottom flask equipped with a magnetic stir bar and an addition funnel. The white cloudy mixture was treated with a solution of oligosalicylate (5.20 g, 42.9 mmol 1.15 eq) and dioxane (20 mL), added over five minutes. The addition funnel was replaced with a condenser, and the reaction mixture was heated to 90 degrees C for 3 hours (at which time the reaction was determined to have finished, by HPLC). The clear orange reaction mixture was cooled to 40 degrees C, filtered and acidified to pH = 1 with 3% (by vol.) aqueous hydrochloric acid. All of the dioxane and some of the water were stripped (60 degrees C, 50mm). The solid (which precipitated from solution during stripping) was isolated by filtration while still warm. The light pink solid was

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recrystallized from 50 mL of 65% ethanol-water. The solid was recovered by filtration and was dried over 18 hours in a 50 degrees C vacuum oven. The N-(salicyloyl)-8-aminocaprylic acid was isolated as a white solid (5.35 g, 51%).

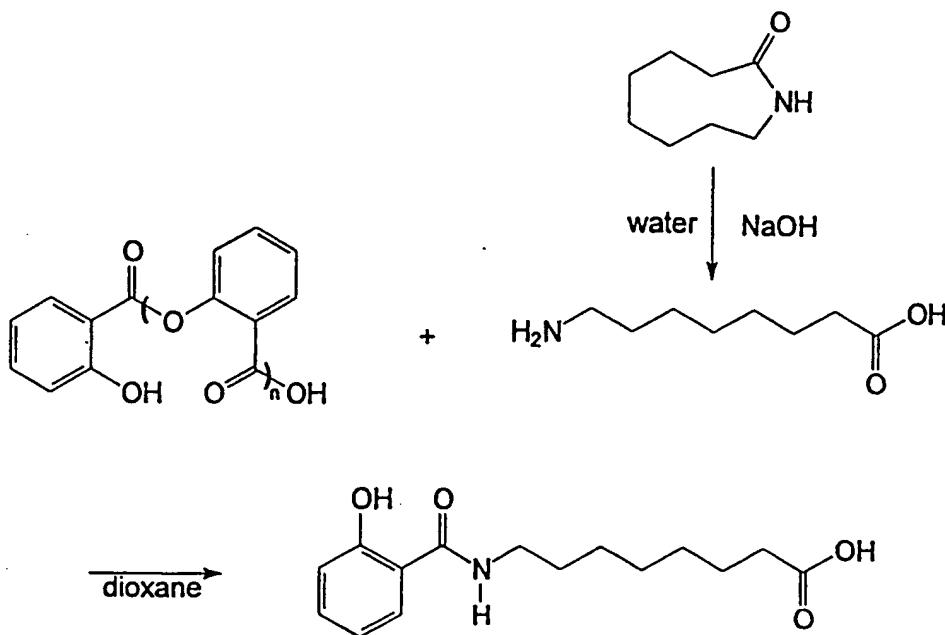
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F. Preparation of Salicyloylamino acid

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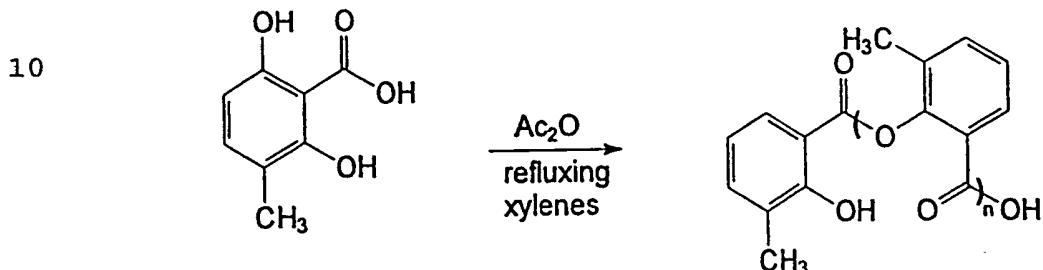


Sodium hydroxide (1.68 g, 42.0 mmol, 1.2 eq), 25.0 g, 35.5 mmol, 1.0 eq) and 20 mL of water were placed a 100 mL round bottom flask equipped with a 25 magnetic stir bar and cold water condenser to prepare aminocaprylic acid. The reaction mixture was heated to reflux for 2.5 hours (at which time the reaction was determined to have finished, by TLC) and cooled to 25 degrees C. A solution of oligosalicylate (4.87g, 40 mmol, 1.1 eq) and dioxane (50 mL) 30 was added to the aqueous solution of 8-aminocaprylic acid. This mixture was heated to reflux for 2.25 hours (at which time the reaction was determined to have finished, by HPLC). The clear orange reaction mixture was cooled to 25 degrees C and acidified to pH = 1 with 3% (by vol.) aqueous hydrochloric acid. All the dioxane and some of the water were stripped (60 degrees C, 50 min). The aqueous phase was decanted from the brown oil while still warm. Crystallization of the oil from ethanol-water yielded a white precipitate. The solid was

recovered by filtration and was dried over 4 hours in a 50 degrees C vacuum oven. The N-(salicyloyl)-8-aminocaprylic acid was isolated as a white solid (5.73g, 59%).

5 Example 2 - Preparation of Oligo(3-methylsalicylate)

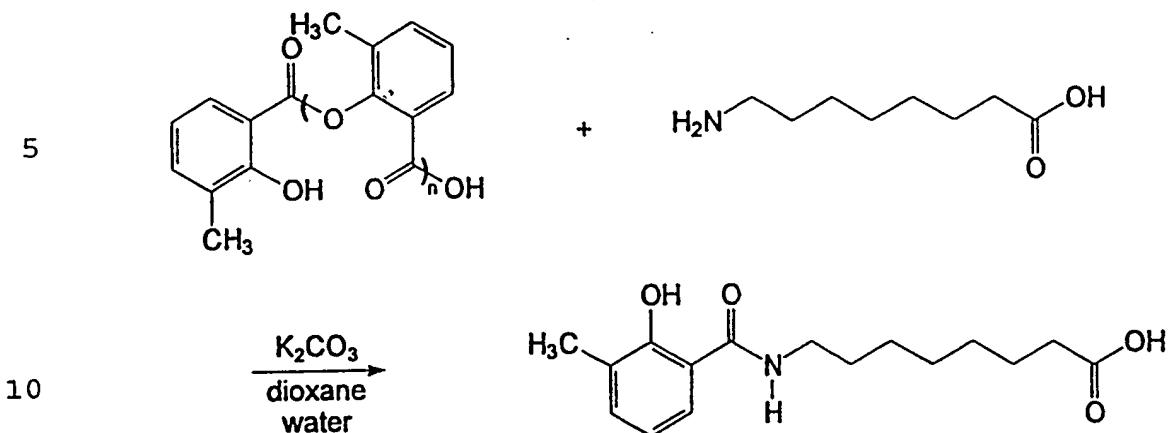
A. Preparation of Oligo N-(3-methylsalicyloyl)-8-aminocaprylic Acid



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Acetic anhydride (11.10 mL, 12.01 g, 0.118 mol, 1.03 eq), 3-methylsalicylic acid (17.37 g, 0.114 mmol, 1.00 eq), and xlenes (60 mL) were added to a 250 mL, three-neck flask fitted with a magnetic stir bar, a thermometer, and a Dean-Stark trap with condenser. The flask was placed in a sand bath and heating of the cloudy white mixture was begun. The reacion mixture cleared to a yellow solution around 100 degrees C. Most of the volatile organics (xlenes and acetic acid) were distilled into the Dean-Stark trap over three hours (135-146 degrees C). Distillation was continued for another hour (a total of 75 mL distilled), during which the pot temperature slowly rose to 175 degrees C and the distillate slowed to a trickle. The residue was poured off while still hot into an aluminum tray. Upon cooling a brittle yellow glass formed. The solid was ground to a fine powder. The 15.90 g of oligo(3-methylsalicylate) produced was used without further purification.

B. Preparation of Salicyloylamino acid



A 50% (by weight) solution of potassium carbonate (24 mL, 36 g, 0.127 mol, 1.23 eq), 8-aminocaprylic acid (16.44 g, 0.103 mol, 1.00 eq), and water (20 mL) were added to a 250 mL round bottom flask equipped with a magnetic stir bar and an addition funnel. The white cloudy mixture was treated with a solution of oligo(3-methylsalicylate) (I 5.90 g, 0.114 mmol 1.11 eq) and dioxane (90 mL), added over five minutes. The addition funnel was replaced with a condenser, and the reaction mixture was heated to 90 degrees C for 4 hours (at which time the reaction was determined to have finished, by HPLC). The clear orange reaction mixture was cooled to 40 degrees C and acidified to pH = 1 with 3% (by vol.) aqueous hydrochloric acid. All the dioxane and some of the water were stripped (60 degrees C, 50mm). The water layer from the resulting two-phase mixture was decanted while still warm. The orange oil was crystallized from 65% ethanol-water to give a tan solid upon cooling to -10 degrees C. The solid was recrystallized from 50 mL of 65% ethanol-water. The off-white solid was washed with hot water (30 mL) to remove most of the remaining salicylic acid. The solid was recovered by filtration and was dried over 6 hours in a 50 degrees C vacuum oven. The N-(3-methylsalicyloyl)-8-aminocaprylic acid was isolated as a light tan solid (12.32 g, 41%).

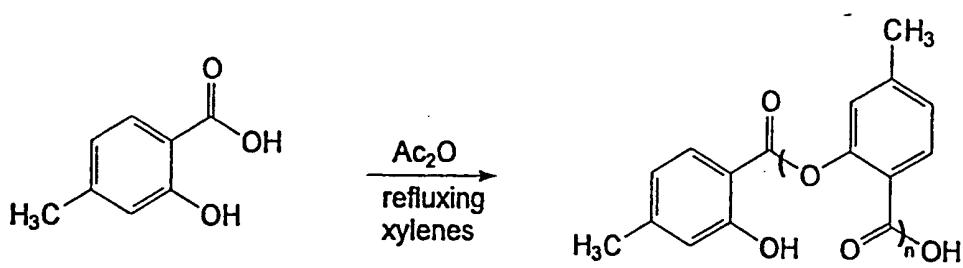
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Example 3 - Preparation of N-(4-methylsalicyloyl)-8-aminocaprylic acid

A. Preparation of Oligo(4-methylsalicylate)

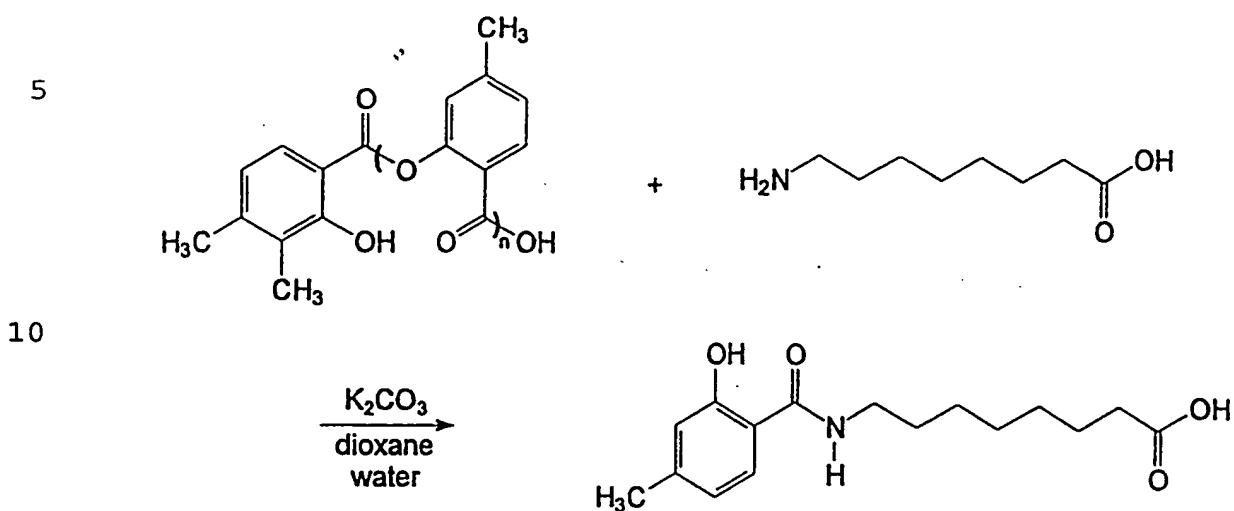
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Acetic anhydride (14.60 mL, 15.80 g, 0.155 mol, 1.04 eq), 4-methylsalicylic acid (22.68 g, 0.149 mmol, 1.00 eq) and xylanes (90 mL) were added to a 250 mL, three-neck flask fitted with a magnetic stir bar, a thermometer, and a Dean-Stark trap with condenser. The flask was placed in a sand bath and heating of the cloudy white mixture was begun. The reaction mixture cleared to a yellow solution around 90°C. Most of the volatile organics (xylanes and acetic acid) were distilled into the Dean-Stark trap over three hours (135-146 degrees C). Distillation was continued for another hour (a total of 110 mL distilled), during which the pot temperature slowly rose to 183 degrees C and the distillate slowed to a trickle. The residue was poured off while still hot into an aluminum tray. Upon cooling a brittle yellow glass formed. The solid was ground to a fine powder. The 20.65 g of oligo(4-methylsalicylate) received was used without further purification.

B. Preparation of Salicyloylamino acid



A 50% (by weight) solution of potassium carbonate (30 mL, 44.6 g, 0.161 mol, 1.19 eq), 8-aminocaprylic acid (21.43 g, 0.135 mol, 1.00 eq), and water (20 mL) were added to a 250 mL round bottom flask equipped with a magnetic stir bar and an addition funnel. The white cloudy mixture was treated with a solution of oligo(4-methylsalicylate) (20.65 g, 0.152 mmol 1.13 eq) and dioxane (80 mL), added over five minutes. The addition funnel was replaced with a condenser, and the reaction mixture was heated to 90 degrees C for 4 hours (at which time the reaction was determined to have finished, by HPLC). The clear orange reaction mixture was cooled to 30 degrees C and acidified to pH = 1 with 3% (by vol) aqueous hydrochloric acid. All of the dioxane and some of the water were stripped (600C, 50mm). The solid (which precipitated from solution during stripping) was isolated by filtration while still warm. The light pink solid was recrystallized from 80 mL of 65% ethanol--water. The solid was recovered by filtration and was dried over 18 hours in a 50 degree C vacuum oven. The N-(4-methylsalicyloyl)-8-aminocaprylic acid was isolated as a white solid (20.40g, 52%).

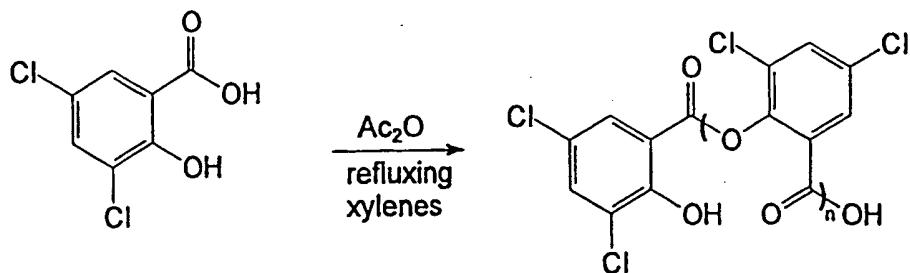
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Example 4 - Preparation of 3-(4-(3,5-dichlorosalicyloyl)aminophenyl)propionic acid

A. Preparation of Oligo(3,5-dichlorosalicylate)

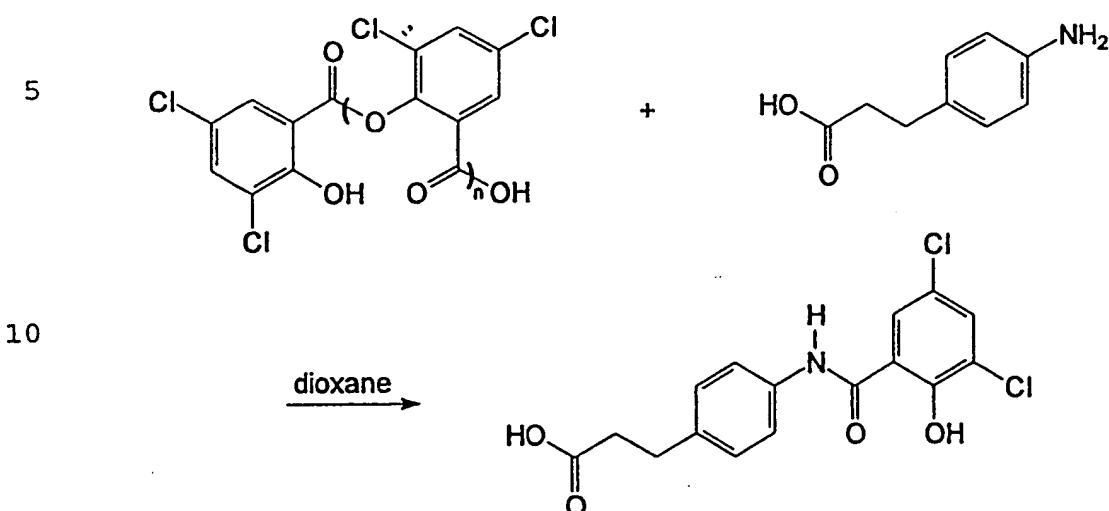
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3,5-dichlorosalicylic acid (15.00 g, 0.073 mol, 1.0 equiv), acetic anhydride (7.69 g, 0.075 mol, 1.04 equiv), and xlenes (40 mL) were added to a 100 mL, three neck flask fitted with an argon purge, a magnetic stir bar, a thermometer, a Dean-Stark trap, and a cold water condenser. The flask was placed into a sand bath, and heating of the cloudy, off white reaction mixture was started. At 115°C the reaction mixture cleared and a xylene/acetic acid mixture began to distill into the Dean-Stark trap at around 130-135 degrees C. Heating continued until most of the xlenes had distilled (approximately 40 mL of liquid was collected) and the reaction mixture thickened and became opaque brown in appearance. At this point, the temperature of the reaction mixture was 175 degrees C, and heating was stopped. The reaction mixture was allowed to cool to room temperature and a tan solid was isolated. The tan solid dried under vacuum for several days to give 15.3g of oligo(3,5-dichlorosalicylate). 12.00 g of this material was carried on to the next step.

B. Preparation of Salicyloylamino acid



Oligo(3,5-dichlorosalicylate) (12.00g, 0.070 mol, 1.10 equiv), 3-(4-aminophenyl) propionic acid (9.42 g, 0.057 mol, 1.0 equiv) and dioxane (150 mL) were added to a 500 mL round bottomed flask fitted with a magnetic stir bar, an argon purge, and a cold water condenser. A tan slurry was formed, and heating was started. The reaction mixture was heated at reflux for 3.5 hr. before being allowed to cool to room temperature. Dioxane was removed under vacuum leaving a brown residue. The brown residue was taken up in aqueous sodium hydroxide (2M, 200 mL). This mixture was filtered, extracted with ethyl acetate (350 mL), and acidified with 2N hydrochloric acid solution. A tan solid precipitated and was isolated by filtration. The tan solid was heated to boiling in a solution of ethanol (100 mL) and water (100 mL). Ethanol was then added to the boiling mixture until a clear solution was obtained. Activated charcoal was added, and the mixture was filtered. Upon cooling a white solid precipitated and was isolated by filtration. The white solid was dried overnight in a vacuum oven at 50 degrees C. The dried 3-(4-(3,5-dichlorosalicyloyl)aminophenyl)propionic acid was isolated as a white solid (9.30 g, 46.0%); mp >225 degrees C; ¹H NMR (DMSO-d6) δ 12.9 (s, 1H), 10.6 (s, 1H), 8.15 (d, 1H), 7.8 (d,

(t, 2H). Anal. Calcd for C₁₆H₁₃Cl₂NO₄: C, 54.24; H, 3.67; N, 3.95. Found: C, 54.21; H, 3.68; N, 3.89.

The above mentioned patents, applications, test methods, and publications are hereby incorporated by reference 5 in their entirety.

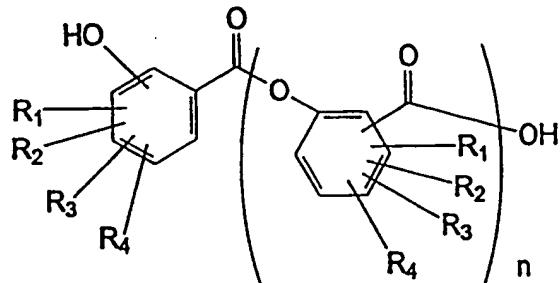
Many variations of the present invention will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the full intended scope of the appended claims.

IN THE CLAIMS:

1 1. A method for preparing a salicyloylamino acid,
2 said method comprising:

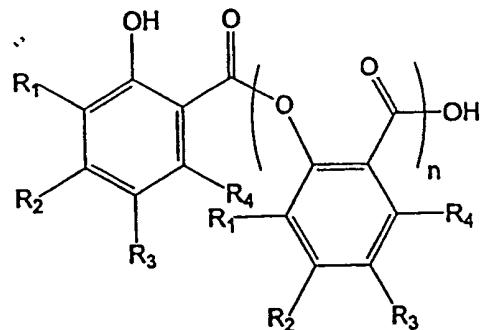
3 (A) reacting an oligosalicylate and an amino
4 acid to yield said salicyloylamino acid.

1 2. A method as defined in claim 1, wherein said
2 oligosalicylate has the formula:



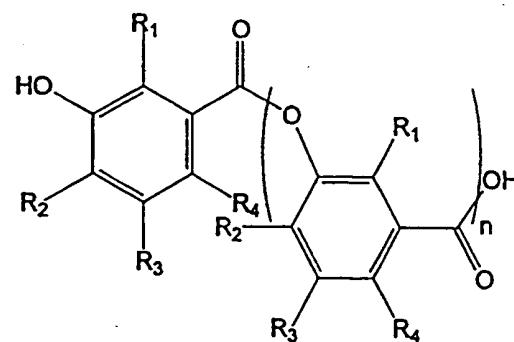
4 wherein R₁, R₂, R₃ and R₄ are independently hydrogen, fluorine,
5 chlorine, bromine, iodine, C₁, linear or branched chain alkyl,
6 C₁₋₉, linear or branched chain alkoxy, C₆₋₁₄ aryl, C₆₋₁₄ aryloxy or
7 (C₆₋₁₄ aryl) (C₁, linear or branched chain alkyl); and wherein n
8 is an integer from about 1 to about 10.

1 3. A method as defined in claim 2, wherein said
2 oligosalicylate has the formula:



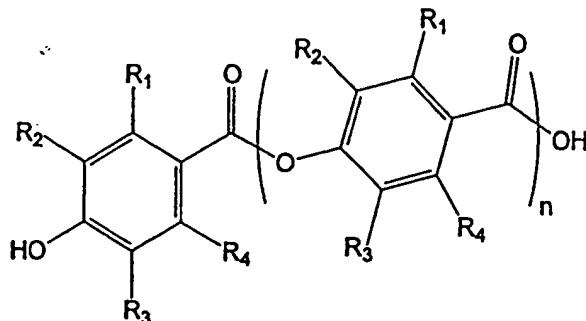
3 wherein R₁, R₂, R₃ and R₄ are independently hydrogen, fluorine,
4 chlorine, bromine, iodine, C₁₋₉ linear or branched chain alkyl,
5 C₁₋₉ linear or branched chain alkoxy, C₆₋₁₄ aryl, C₆₋₁₄ aryloxy or
6 (C₆₋₁₄ aryl) (C₁₋₉ linear or branched chain alkyl); and wherein n
7 is an integer from about 1 to about 10.

1 4. A method as defined in claim 2, wherein said
2 oligosalicylate has the formula:



3 wherein R₁, R₂, R₃ and R₄ are independently hydrogen, fluorine,
4 chlorine, bromine, iodine, C₁₋₉ linear or branched chain alkyl,
5 C₁₋₉ linear or branched chain alkoxy, C₆₋₁₄ aryl, C₆₋₁₄ aryloxy or
6 (C₆₋₁₄ aryl) (C₁₋₉ linear or branched chain alkyl); and wherein n
7 is an integer from about 1 to about 10.

1 5. A method as defined in claim 2, wherein
2 said oligosalicylate has the formula:

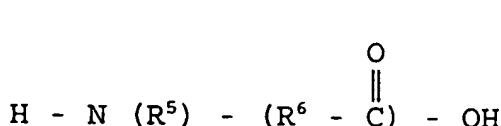


3 wherein R₁, R₂, R₃ and R₄ are independently hydrogen, fluorine,
4 chlorine, bromine, iodine, C₁-, linear or branched chain alkyl,
5 C₁-, linear or branched chain alkoxy, C₆₋₁₄ aryl, C₆₋₁₄ aryloxy or
6 (C₆₋₁₄ aryl)(C₁-, linear or branched chain alkyl); and wherein n
7 is an integer from about 1 to about 10.

1 6. A method as defined in claim 2, wherein said
2 oligosalicyloyl is selected from the group consisting of
3 oligosalicylate, oligo-methyl salicylate, and oligo-
4 dichlorosalicylate.

1 7. A method as defined in claim 1, wherein said
2 amino acid is selected from the group consisting of natural
3 amino acids and non-natural amino acids.

1 8. A method as defined in claim 7, wherein said
2 amino acid has the formula:



7 wherein: R⁵ is hydrogen, C₁-C₄ alkyl, or C₂-C₄ alkyl, or C₂-C₄ alkenyl;

9 R⁶ is C₁-C₂₄ alkyl, C₂-C₂₄ alkenyl, C₃-C₁₀ cycloalkyl,
10 phenyl, naphthyl, (C₁-C₁₀ alkyl) phenyl, (C₂-C₁₀
11 alkenyl) phenyl (C₁-C₁₀ alkyl) naphthyl, (C₂-C₁₀
12 alkenyl) naphthyl, phenyl (C₁-C₁₀ alkyl) phenyl

23 R⁶ being optionally interrupted by oxygen, nitrogen,
24 sulfur, or any combination thereof; and

25 R⁷ is hydrogen, C₁-C₄ alkyl, or C₂-C₄ alkenyl.

1 9. A method as defined in claim 8, wherein said
2 amino acid is selected from the group consisting of alanine,
3 arginine, asparagine, citrulline, cysteine, cystine, glutamine,
4 glycine, histidine, isoleucine, leucine, lysine, methionine,
5 ornithine, phenylalanine, proline, serine, threonine,
6 tryptophan, tyrosine, valine, hydroxy proline, γ -
7 carboxyglutamate, phenylglycine, O-phosphoserine, β -alanine,
8 α -amino butyric acid, γ -amino butyric acid, γ -(aminophenyl)
9 butyric acid, α -amino isobutyric acid, citrulline, ϵ -amino
10 caproic acid, 7-amino heptanoic acid, β -aspartic acid,
11 aminobenzoic acid, aminocaprylic acid, aminophenyl acetic acid,
12 aminophenyl butyric acid, γ -glutamic acid, cysteine (ACM), ϵ -
13 lysine, ϵ -lysine (A-Fmoc), methionine sulfone, norleucine,
14 norvaline, ornithine, d-ornithine, p-nitro-phenylalanine,
15 hydroxy proline, 1,2,3,4,-tetrahydroisoquinoline-3-carboxylic
16 acid, aminodecanoic acid, and thioproline.

1 10. A method as defined in claim 9, wherein said
2 amino acid is aminocaprylic acid.

1 11. A method as defined in claim 2, wherein said
2 oligosalicylate is oligo-n-salicylate, said amino acid is
3 aminocaprylic acid, and said salicyloylamino acid is N-
4 (salicyloyl)-8-aminocaprylic acid.

1 12. A method as defined in claim 2, wherein said
2 reacting is conducted in an aqueous medium.

1 13. A method as defined in claim 12, wherein said
2 aqueous medium comprises water.

1 14. A method as defined in claim 13, wherein said
2 aqueous medium further comprises sodium hydroxide.

1 15. A method as defined in claim 14, wherein said
2 aqueous medium further comprises an organic solvent selected
3 from the group consisting of dioxane, xylene, acetonitrile,
4 tetrahydrofuran, and 1-methoxy-propanol.

1 16. A method as defined in claim 2, wherein said
2 reacting occurs at a temperature ranging from about 25 to about
3 150°C.

1 17. A method as defined in claim 2, wherein the
2 molar ratio of said oligosalicylate to said amino acid ranges
3 from about 0.5 to about 2.0.

1 18. A method as defined in claim 2, wherein said
2 reaction is allowed to take place for about 0.5 to about 24
3 hours.

1 19. A method as defined in claim 2, further
2 comprising
3 (B) isolating said salicyloylamino acid.

1 20. A method as defined in claim 19, wherein said
2 isolating comprises filtering.

1 21. A method as defined in claim 20, wherein said
2 isolating further comprises drying.

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